Synthesis and Antibacterial Activity of Some Novel Schiff 's-Bases Compounds Containing Oxadiazle Ring

J. H. Tomma , A. H. Raheema* and I. H. Rouil
Department of Chemistry , College of Education , Ibn Al-Haitham University of Baghdad
***Science and Technology Ministry**

Abstract

Condensation of 4-methoxybenzoyl hydrazine with 4-aminobenzoic acid in the presence of $POCl_3$ gave the oxadiazole derivative [III] .This compound was demethylated with aluminum chloride to give series of 2- (4-hydroxy phenyl)-5-(4-amino phenyl)-1,3,4-oxadiazole [IV] . Series of Schiff 's bases $[V]_n$ were synthesized by the condensation of compound [IV] with 4-n-alkoxy benzaldehyde in the presence of glacial acetic acid. Condensation of compounds $[V]_n$ with adipoyl chloride in dry pyridine leads to the formation of a new homologous series $[VI]_n$.The structures of the synthesized compoumds were confirmed by physical and spectral means .

The new compounds $[VI]_n$ have been screened for their antibacterial activities . The results showed considerable antibacterial activity against *Escherichia Coli* (G-),but did not show any antibacterial activity against *Staphylococus aureus* (G+) .

Introduction

1,3,4-Oxadiazole derivatives play an important role in organic synthesis , since most of compounds of the this type possess diverse biological activities , such as antifungal (1),anticonvulsant(2),anti-inflammatory (3) and antibacterial activities .

Amir et al., prepared a new compound of the 2-ethyl thio-5-[4-(hydroxyl benzylidene amino)phenyl]-1,3,4-oxadiazol has shown antibacterial activity against *E.coli* and *S.aureus* [4] .

Recently, three compounds of 5,5-dimercapto-bis-[1,3,4-oxadiazol-2-yl] alkane exhibited both antibacterial and antifungal activities against *S.aureus* and *B.subtilis* [5] .

Schiff 's bases are important compounds since they have biological activity against bacteria and fungi. 2-alkylthio-5-benzylidene amino-thiazol has been shown to be strong antibacterial and antifungal [6] . Also, the Schiff 's bases posses anticancer (7,8) activity in animal screening .

Based on these findings , synthesis of some novel oxadiazole derivatives were carried out for the purpose of evaluation as antibacterial agent.

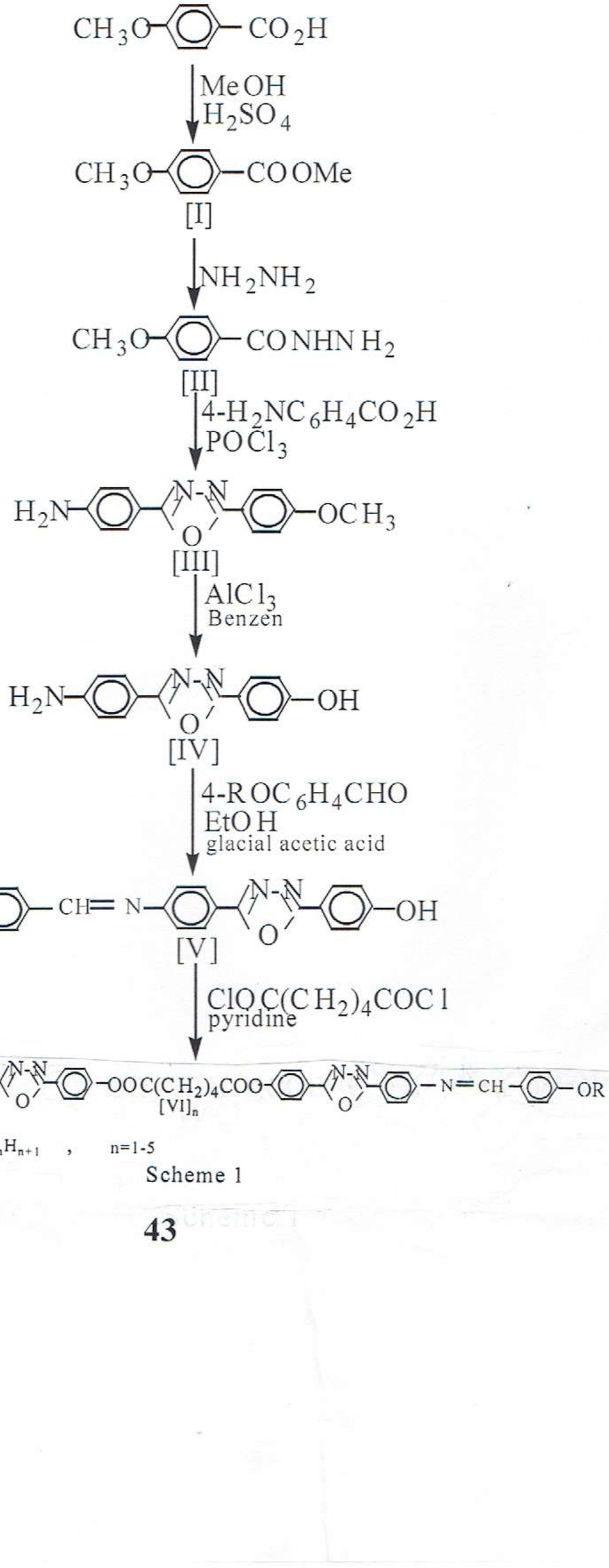
Experimental

Materials : Most of chemicals used were supplied from Fluka and BDH Chemicals Co. and used as received .

Techiques: The melting points were recorded by using an (Electrothermal) melting point apparatus . Elemental analysis were carried out by using Carlo-Erba 5500 elemental analyzer . The IR spectra were recorded on a PYE-UNICAM type (1310) infrared spectrophotometer using potassium bromide discs, and the FTIR were recorded on a Schimadzu FTIR-8300 fourier transforn infrared spectrophotometer . Ultra-violate spectra were recorded on a Shimadzu UV-Visible-160 spectrophotometer .

Synthesis

The reaction sequence leading to the formation of different title compounds are outlined in Scheme 1.



R=C_nH_{n+1} , n=1-5

Scheme 1

Methyl 4-methoxy benzoate [I] : was prepared following the procedure described by Vogel (9) .
m.p. : 49-51 °C (Lit. m.p. : 49-51 °C) .

4-Methoxy benzoyl hydrazine [II] : was prepared following the procedure described by Smith (10) . m.p. : 135-137 °C .

2-(4-Methoxyphenyl)-5-(4-aminophenyl)-1,3,4-oxadiazole [III]

A mixture of 4-methoxybenzoyl hydrazine (0.01mol), 4-amino benzoic acid (0.01 mol) and phosphorus oxy chloride (5mL) was refluxed for 7 hrs . The cold reaction mixture was poured into ice-water and made basic by adding sodium bicarbonate solution . The formed solid was filtered , dried and purified by refluxing with ethanol (11) , yield (89%) , m.p. 196 °C .
Elemental analysis : $C_{15}H_{13}N_3O_2$; Found : C%=67.89 , H%=5.44 , N%=15.49 : Calcd. : C%=67.41 , H%=4.86 , N%=15.73 .

2-(4-Hydroxyphenyl)-5-(4-aminophenyl)-1,3,4-oxadiazole [IV]

The anhydrous aluminum chloride (1gm) was added to the compound [III] (.09 gm,0.033 mol) that was dissolved in dry benzene 25 mL.The reaction mixture was refluxed for 10 hrs . The solvent was evaporated and the residue was poured into ice water . The solid was formed, collected and purified by dissolving in 30 ml of 10% NaOH solution . The remainder solid was filtered and the filtrate was neutralized with 10% HCl . The crude product precipitate during the neutralization was collected by filtration ,washed with water several times and dried to give the desired compound [IV] (12) , yield 90% , m.p. >300 °C .

2-(4-Hydroxyphenyl)-5-[(4-(4´-alkoxybenzylidene)amino phenyl]-1,3,4-oxadiazole[V]$_n$

A mixture of compound [IV] (0.01 mol) , 4-alkoxybenzaldehyde (0.01 mol) , absolute ethanol (15 mL) and glacial acetic acid (5 drops) was refluxed for 48 hrs . The solvent was evaporated and the residue was poured into ice water . The resulting precipitate was collected and recrystalized from chloroform . The physical properties for the synthesized compounds are given in table 1 .

Bis2-[5-{4-(4´-n-alkoxybenzylidene)aminophenyl}-1,3,4-oxadiazolyl]-4´-phenyl adipate [VI]$_n$

To a stirred solution of compound [V]$_n$ (0.02 mol) , dry pyridine (5mL) was added dropwise adipoyl chlorid (0.01 mol) at 4 °C . After

addition has been completed, the resulting mixture was stirred at the same temperature for 5 hrs . Afterwards, the mixture was poured into 100 mL of 10% HCl . The precipitate was formed , filtered and washed with solution of 10% $NaHCO_3$, then washed with water several times , dried and recrystallized from acetone . The physical properties of the new synthesized compounds are given in table 2.

Results and Discussion

Methyl-4-methoxy benzoate [I] was obtained by esterification of 4-methoxy benzoic acid (Anisic acid) with methanol . The reaction of 4-methoxy methyl benzoate with hydrazine hydrate in ethanol under reflux gave 4-methoxy benzoyl hydrazine [II] in 95% yield . Condensation of acid hydrazide [II] with 4-aminobenzoic acid in the presence of dehydrating agent phosphorus oxychloride yielded the oxadiazole derivative [III] . The structure of this compound was confirmed by elemental analysis and spectral data (IR , FTIR and UV spectra) .

The IR-absorption spectrum of this compound showed disappearance of absorption bands due to C=O stretching (amid) of hydrazide [II] together with the appearance of a stretching band at 1610 cm^{-1} which is assigned to C=N stretching of oxadiazole ring . It also shows two peaks at 3200 cm^{-1} , 3350 cm^{-1} , which are assigned to the symmetric and asymmetric stretching bands of NH_2 group and at 1070 cm^{-1} , 1245 cm^{-1} due to symmetrical and asymmetrical C-O-C stretching vibration . FTIR-spectrum show : two peaks at 3222.8 cm^{-1} and 3344.3 cm^{-1} attributed to the NH_2 group , peak at 3074.3 cm^{-1} due to aromatic CH_2 group , two peaks in the region (2841-2935.5) cm^{-1} due to aliphatic CH_2 group , and a band at 1608.5 cm^{-1} could be attributed to the C=N stretching of vibration of oxadiazole ring . UV spectrum of oxadiazole [III] in DMSO (solvent) [1×10^{-3} mol/L] gives the λ_{max} 305.4 nm (ε_{max}=1.48) .

Compound [III] was demethylated with aluminum chloride to give the desired 2-(4-hydroxyphenyl)-5-(4-amino phenyl)-1,3,4-oxadiazole [IV] .

The synthesized compound was characterized by IR , FTIR and UV spectra .

The characteristic of IR-absorption bands showed the disappearance of absorption bands due to $-CH_3$ aliphatic streching of

[III] together with the appearance of abroad band in the range (3160-3380) cm^{-1} due to hydrogen bonding (O-H) stretching . FTIR spectrum give : 3382.9 cm^{-1} (broad peak of O-H group) ; 1610.5 cm^{-1} (C=N of oxadiazole ring) . UV spectrum of this compound in DMSO (as a solvent) [1×10^{-3} mol/L] gives the λ_{max} 306.2 nm (ε_{max} =0.75) .

The new series of Schiff 's – bases $[V]_n$ was synthesized by condensation of 2-(4-hydroxy phenyl)-5-(4-amino phenyl)-1,3,4-oxadiazole [IV] with 4-alkoxy benzaldehyde . These Schiff 's bases $[V]_n$ were identified by elemental analysis , IR , UV , and FTIR spectroscopy .

IR spectra of these compounds showed the disappearances of two absorption bands due to NH_2 stretching and appearance of absorption band at (1660-1680) cm^{-1} is attributed to the C=N stretching . They also showed bands at (2815-2935) cm^{-1} are due to aliphatic (C-H) stretching . FTIR spectra give : 3295.9 cm^{-1} (broad peak of O-H group); 1660 cm^{-1}(C=N of azomethine group) ; 1606.6 cm^{-1} (C=N of oxadiazole ring) . UV spectra of these compounds were obtained in chloroform [1×10^{-3} mol/L] , the UV data of these compounds (λ_{max}) are given in Table (1) .

The new homologous series $[VI]_n$ were prepared by the reaction of compounds $[V]_n$ with adipoyl chloride .

The structure of compounds $[VI]_n$ identified by IR and FTIR spectra . The IR-spectra of these compounds showed significant peaks in the region (1710 –1720) cm^{-1} attributed to the streching vibration of the carbonyl of the ester group and two peaks at (1170-1250) cm^{-1} could be attributed to the O=C-O bending .They also showed the disappearance of absorption bands due to O-H streching of compounds $[V]_n$. Other peaks are given in Table 3 . FTIR spectra exhibited : 2927.7 cm^{-1} (CH_2 aliphatic) ; 1715 cm^{-1} (C=O of ester group) ; (1255.6 and 1174.6) cm^{-1} (two peaks of O-C=O) ; 1660 cm^{-1} (C=N of azomethine group) ; 1604.7 cm^{-1} (C=N of oxadiazole ring) .

Biological Activity

Synthesised $[IV]_n$ series of compounds have been screened for their antibacterial activity by agar growth technique against two type of bacteria viz., *Escherichia Coli* (Gram-negative bacteria) and *Staphylococcus* (Gram-positive bacteria) .The diameter of the bacteria colony was measured at three different concentrations 0.1mg/mL , 0.01mg/mL , 0.001 mg/mL . The plates were incubated for 24 hrs at 37

°C. The zone of inhibition formed was measured in mm and are represented by (+) , (++) , (+++) depending upon the diameter and clarity . The results of the preliminary screening test are listed in Table 4 . From the data obtained in Table 4 , it is clear that all the tested compounds showed biological activity against *E. Coli* . Most of the tested compounds were found to be highly active at higher concentration 0.1 mg/mL, while slightly active and moderately active at 0.001 mg/mL concentration . But all these compounds were found to be inactive against *staphylococcus aureus* (G+) . In this series $[VI]_n$,the antibacterial activity showed a slight increase as the number of carbon atom in the terminal group (OR) .

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Table (1) The physical properties and UV data of the compounds $[V]_n$.

Comp. No.	Formula	m.p. (°C)	Yields (%)	Color	λ_{max} (nm)
$[V]_1$	$C_{22}H_{17}N_3O_3$	152	85	Pale yellow	308.6
$[V]_2$	$C_{23}H_{19}N_3O_3$	162	88	Yellow	312.0
$[V]_3$	$C_{24}H_{21}N_3O_3$	178	84	Yellow	309.4
$[V]_4$	$C_{25}H_{23}N_3O_3$	174	90	Brown	315.9
$[V]_5$	$C_{26}H_{25}N_3O_3$	184	79	Brown	323.4

Table 2) The physical properties of the compounds $[VI]_n$.

Comp. No.	Formula	m.p. (°C)	Yields (%)	Color
$[VI]_1$	$C_{50}H_{40}N_6O_8$	138	84	Brown
$[VI]_2$	$C_{52}H_{44}N_6O_8$	148	90.5	Brown
$[VI]_3$	$C_{54}H_{48}N_6O_8$	160	89	Brown
$[VI]_4$	$C_{56}H_{52}N_6O_8$	135	85	Brown
$[VI]_5$	$C_{58}H_{56}N_6O_8$	125	80	Brown

Table (3) Characteristic IR absorption bands of series $[VI]_n$.

Comp. No.	Characteristic bands IR spectra (cm^{-1})				
	νC-H Aliph.	νC=O Ester group	νC=N of Azomethine group	νC=N of Oxadiazole ring	δO=C-O
$[VI]_1$	2850-2915	1715	1655	1600	1170 , 1245
$[VI]_2$	2855-2920	1715	1660	1600	1165 , 1250
$[VI]_3$	2855-2915	1710	1655	1600	1170 , 1250
$[VI]_4$	2860-2920	1710	1655	1600	1170 , 1255
$[VI]_5$	2850-2925	1710	1660	1600	1170 , 1255

Table (3) Results of antibactrial activity of the tested compounds $[VI]_n$ at different concentrations.

Comp. No.	*Escherichi coli* (G-)			*Staphylococcus aureus* (G+)		
	Concentration mg/mL			Concentration mg/mL		
	0.001	0.01	0.1	0.001	0.01	0.1
$[VI]_1$	+	++	++	-	-	-
$[VI]_2$	+	++	+++	-	-	-
$[VI]_3$	+	+++	+++	-	-	-
$[VI]_4$	++	+++	+++	-	-	-
$[VI]_5$	++	+++	+++	-	-	-

Key to symbols : Highly active (+++) > 12 mm ,Moderately active (++)= 9-12 mm , Slightly active (+) =5-8 mm , Inactive(-) < 5 .

تحضير ودراسة الفعالية البايولوجية لبعض من قواعد شف الجديدة المحتوية على حلقة اوكسادايازول

جمبد هرمز توما ، علي حسين رحيمة*، ايفان حميد روئيل
قسم الكيمياء، كلية التربية- ابن الهيثم ، جامعة بغداد
***وزارة العلوم والتكنولوجيا**

الخلاصة

ي يحضرالمركب 2- (4َ-ميثوكسي فنيل)-5-(4َ - امينو فنيل)-4,3,1 - اوكسادايازول [III] من تكاثف 4-ميثوكسي بنزوايل هيدرازين مع 4-امينوحامض البنزويك بوجود $POCl_3$. يتفاعل المركب [III] المحضر مع كلوريد الالمنيوم ليعطي المركب 2- (4َ -هيدروكسي فنيل) -5- (4َ – امينوفنيل) - 4,3,1- اوكسادايازول [IV] . تم الحصول على قواعد شف $[V]_n$ من تفاعل المركب الاخير [IV] مع 4-ن-الكوكسي بنزالديهايد بوجود حامض الخليك الثلجي . حضرت السلسلة الجديدة $[VI]_n$ من تفاعل قواعد شف المحضرة في هذه الدراسة مع ثنائي كلوريد الحامض الكاربوكسيلي (كلوريد الاديبويل) في البيريدين الجاف بدرجة $4\ ^{o}C$. شخصت المركبات المحضرة باستخدام التحليل الدقيق للعناصر والقياسات الطيفية .لقد تمت دراسة الفعالية البايولوجية لجميع مركبات السلسلة الجديدة $[VI]_n$] باستخدام نوعين من البكتريا coli (G-) و Echerichia Staphylococcus aureus(G+) ، واظهرت فعالية بايولوجية ضد النوع الاول من البكتريا (G-) ولم تظهر أي فعالية بايولوجية تجاه النوع الاخر (G+) .